

Application No.: 10/658,962  
Attorney Docket No.: 49321-008US0  
First Applicant's Name: Mendy S. Maccabee  
Application Filing Date: September 8, 2003  
Final Office Action Dated: August 16, 2010  
Date of Response: February 16, 2011  
Examiner: Jennifer M. Kim

### **REMARKS**

Claims 1, 6-8, 21, and 24-28 are pending and stand rejected.

No claims have been amended by this Response.

New claim 29, fully supported by the originally-filed specification has been added.

No new matter has been added.

#### ***Claim Rejections-35 USC §103(a)***

Claims 1, 6-8, 21, and 24-28 stand rejected, under 35 U.S.C. §103(a), as allegedly being obvious over Shigeyama (*Vitamin A Metabolism In Nasal and Paranasal Diseases*, 1968; already of record) (hereinafter "Shigeyama"), in view of Biesalski (U.S. Pat. No. 5,556,611; already of record) (hereinafter "Biesalski"), Belloni (U.S. Pat. No. 6,339,107; already of record) (hereinafter "Belloni"), and Popp et al. (*Pretreatment of photoaged forearm skin with topical tretinoin accelerates healing of full-thickness wounds*, 1995) (hereinafter "Popp"), and further in view of Heiber et al. (U.S. Patent No. 5,766,620) (hereinafter "Heiber") for reasons as stated in the Office Action (hereinafter "OA").

#### ***Shigeyama:***

Briefly, the Examiner states that the primary reference "Shigeyama teaches that the patients having chronic paranasal sinusitis were injected with water-soluble vitamin A palmitate (Chokola A) by intramuscular injection. Shigeyama teaches that vitamin A is mainly distributed in the epithelial layer, gland tissue and vessels. Shigeyama teaches that their findings revealed that serum vitamin A decreased in chronic paranasal sinusitis patients, suggesting that reduced vitamin A levels caused local regressive changes in mucosa that facilitated infection, and exerted a steady influence on the autonomic nervous system that facilitated allergic changes. These findings also suggest that

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poor circulation formed between decreased vitamin A and local lesions and also liver function, which simultaneously acted causally to partially inhibit curing and foster development of a chronic condition. (pages 37 first paragraph, 40, 41, 58, 79 first full paragraph, 101" (emphasis added by Applicants).

Applicants respectfully point out that the Examiner's own articulated teachings of Shigeyama explicitly defeat any alleged *prima facie* case of obvious, because Shigeyama *teaches away* from the presently claimed invention by teaching that multiple factors and tissues act simultaneously and systemically to mediate development of chronic paranasal sinusitis in patients, and one of skill in the art would, therefore, conclude that systemic vitamin A administration would be the only reasonably effective route of treatment as discussed below in more detail.

Specifically, while Shigeyama may teach that chronic paranasal sinusitis patients have slightly decreased serum vitamin A, and that giving *systemic* vitamin A to infants suffering from paranasal sinusitis had a curing effect in light cases, Shigeyama explicitly teaches, as acknowledged above by the Examiner, that multiple systemic factors act simultaneously to causally inhibit curing and foster development of a chronic condition; namely:

- serum vitamin A levels;
- changes in mucosa and infection;
- poor circulation;
- steady influence by the autonomic nervous system that facilitates allergic changes; and
- liver function.

Applicants respectfully further point out the Shigeyama also teaches (see Shigeyama at pages 33-38) that:

- inflammation;
- nutrition;
- endocrinopathy;
- metabolic disorders;
- anemia;
- allergies;
- poor hygiene;
- parasympathetic nerve hypertonicity and vagal nerve involvement; and

-bacterial and/or viral infection

may be considered “systemic factors.” At page 35, for example, Shigeyama discusses that Ozawa teach the relation of chronic paranasal sinusitis to liver function. At page 36, Shigeyama discusses that Tamara teaches involvement of parasympathetic nerve hypertonicity, and involvement of a “large number of allergic factors in the hepatopathy group,” and vagal nerve involvement. Shigeyama states, at page 98, that “vitamin A metabolism is subject to damage when there is hepatopathy, reducing the capacity to accumulate vitamin A in the liver and reducing blood vitamin A levels.”

The prior art, therefore, including Shigeyama’s portrayal thereof and as recognized by the Examiner, overwhelming recognizes a causal simultaneous involvement of multiple systemic factors (e.g., at least the 14 cited above) in multiple distinct tissue compartments (e.g., mucosa, liver, nerves, endocrine glands, blood, etc.), along with systemic metabolism of vitamin A, in the etiology of chronic paranasal sinusitis.

Not surprisingly, therefore, and entirely consistent with these teachings, Shigeyama explicitly teaches systemic administration of vitamin A (i.e., intramuscular administration) to provide for simultaneously addressing multiple systemic factors and distinct tissue compartments, and given these explicit teachings of Shigeyama, and Shigeyama’s detailed discussion of the systemic factors and multiple distinct tissue compartments (as widely recognized in the prior art), Applicants contend that one of skill in the art would conclude that for effectively treating chronic paranasal sinusitis, systemic administration would be required to have any reasonable chance to simultaneously affect the multiple systemic factors and distinct tissue compartments (e.g., autonomous nervous system, liver, endocrine compartments, mucosa, blood, etc.).

Shigeyama, therefore, and as effectively acknowledged by the Examiner, fundamentally *teaches away* from Applicants’ claimed methods. Shigeyama not only does not support the Examiner’s urged *prima facie* case of obviousness, but it also effectively rebuts and defeats any such *prima facie* case even if considered established.

***Biesalski:***

The Examiner acknowledges that “Shigeyama does not expressly teach topical delivery to sinus cavity, an implant formulations set forth in claims 1 and 6 and the subject had undergone a surgery set forth in claim 27.”

The Examiner, however, asserts that Biesalski teaches “a pharmaceutical preparation consisting of retinoic acid as an active substance suitable for a topical treatment of mucosal disease in man and animal (abstract)” (emphasis added by Applicants). The Examiner states that Biesalski teaches that the preparation is effective for treating functional impairments in the mucous membranes of humans and animals, in particular in the respiratory epithelium and the epithelia of the nose-throat cavity” (emphasis added by Applicants).

Applicants respectfully point out, however, that the teachings of Biesalski are limited to use of aerosol delivery of retinoic acid to treat the epithelium and mucosa of the nose-throat cavity and preferably the “epithelia of the tracheal and deep bronchial tract.” and thus provides no teaching or suggestion whatsoever, of administration of vitamin A to the sinus cavity by any means. See, e.g., column 2, lines 15-20. Applicants contend that this is not surprising because, as appreciated in the relevant art, the passages in the nasal cavity are extremely narrow and twisted with 1-2 mm openings and hairpin turns, such that the vast majority (90%) of the air flow through the nasal cavity is directed down and back directly into the lungs with very little air flow passing through the desired medicament delivery target area of the upper and posterior regions of the nasal cavity, such that there has been a long-standing problem of not being able to effectively deliver medicament to desired target regions, and in particular to the sinus cavities.

Moreover, even if Biesalski was construed, for the sake of argument, to teach administration to sinus mucosa (which it does not teach), it fails to reasonably teach or suggest administration of vitamin A to sinus mucosa from an implant placed in the sinus cavity.

Furthermore, to the extent that Biesalski arguably teaches *local* administration to epithelium and mucosa of the nose-throat cavity and epithelia of the tracheal and deep bronchial tract, it cannot

be reasonably construed to teach efficacy of local administration to sinus mucosa, because this compartment is not targeted or reached by the methods of Biesalski, and **in any event, does not cure the systemic administration limitation of Shigeyama, when the two references are considered in combination.**

***Belloni:***

The Examiner states that Belloni teaches that “topical administration of retinoic acid can be formulated as solutions, gels, ointments, creams, suspension, etc. as are well-known in the art. (column 8, lines 14-17). Belloni teaches that retinoic acid can be formulated for oral liquid preparations such as suspensions, elixirs and solutions, as well as transmucosal and buccal administration. (column 8, lines 35-40, line 40-65, column 9, lines 1-6). Belloni teaches that retinoic acid can be formulated as a depot preparation and can be administered by implantation. (column 10, lines 35-45).”

Applicants respectfully point out, however, that the teachings of Belloni are limited to topical use of 13-cis-retinoic acid to treat lung disorders such as chronic obstructive pulmonary disorders, including chronic bronchitis, emphysema, and asthma. Belloni fails to teach the treatment of sinus disease or promotion of sinus wound healing in subjects in need thereof, and thus does not cure the deficiencies in Biesalski (local non-sinus cavity delivery) and/or Shigeyama (systemic sinusitis) as described above when the references are considered in combination. **Belloni does not cure the systemic administration limitation of Shigeyama, and/or the non-sinus cavity delivery limitation of Biesalski when the three references are considered in any combination together.**

***Popp:***

The Examiner states that Popp teaches that it has been known for decades that vitamin A and its derivatives can enhance various aspects of wound repair. (page 46, left-hand side, first paragraph).

Applicants respectfully point out, however, that the teachings of Popp are limited to treatment of dorsal forearm skin in elderly men having a history of excessive sun exposure with all-trans retinoic acid. Popp, and/or the prior art cited therein, fail to teach the treatment of sinus disease or promotion of sinus wound healing in subjects in need thereof, and thus do not cure the deficiencies in Biesalski (local non-sinus cavity delivery) and/or Shigeyama (systemic delivery for sinusitis) and/or Belloni (topical treatment for lung disorders) as described above when the references are considered in combination. Popp does not cure the systemic administration limitation of Shigeyama, and/or the non-sinus cavity delivery limitation of Biesalski, and/or the non-sinus lung treatment limitation of Belloni when the four references are considered in any combination together.

***Heiber:***

The Examiner states that Heiber teaches that “transmucosal delivery system includes a patch (column 11, lines 35-45).”

Applicants respectfully point out, however, that while Heiber may arguably teach use of a patch for transmucosal delivery of glucagon-like insulinotropic peptide, the teachings of Heiber are strictly limited to delivery of polypeptides via the buccal mucosa of the oral cavity. Heiber fails to teach the treatment (with any agent) of sinus disease or promotion of sinus wound healing in subjects in need thereof, and thus do not cure the deficiencies in Biesalski (local non-sinus cavity delivery), and/or Shigeyama (systemic delivery for sinusitis), and/or Belloni (topical treatment for lung disorders), and/or Popp (topical, dorsal forearm skin) as described above when the references are considered in combination. Heiber does not cure the systemic administration limitation of Shigeyama, and/or the non-sinus cavity delivery limitation of Biesalski, and/or the non-sinus lung treatment limitation of Belloni, and/or the topical, dorsal forearm skin limitation of Popp when the five references are considered in any combination together.

*In summary*, Applicants' claim 1 has previously been amended to recite that the vitamin A composition is topically delivered to a sinus cavity from an implant placed in the sinus cavity.

The cited references, alone or in combination, not only lack disclosure of these limitations, but the primary reference Shigeyama (the only reference to teach treating a sinus cavity condition; sinusitis) explicitly and fundamentally teaches away from the presently claimed invention, by teaching only systemic administration of Vitamin A by intramuscular injection, in view of Shigeyama's teachings that the etiology of chronic paranasal sinusitis involves a causal simultaneous involvement of multiple systemic factors (e.g., at least the 14 cited above) in multiple distinct tissue compartments (e.g., mucosa, liver, nerves, endocrine glands, blood, etc.), along with systemic metabolism of vitamin A, and would, therefore, be construed by one of skill in the art as teaching a requirement for systemic administration to effectively treat chronic paranasal sinusitis. Applicants, contend therefore, that the asserted art, when considered alone or in combination, would provide a disincentive (not a motivation) to one of skill in the art to treat sinus conditions as presently claimed, and does not, therefore, support the Examiner's conclusion at pages 6 and 7 of the Office Action that it would have been obvious (or that there would have been motivation) to administer an effective amount of vitamin A via topical delivery including an implant to a sinus cavity of a subject to provide a reasonable treatment of sinus conditions, which are viewed as simultaneously involving multiple systemic factors and distinct tissue compartments.

Finally, contrary to the Examiner's urging at page 8, Applicants respectfully contend, as argued above, that in view of the causal simultaneous involvement of multiple systemic factors in multiple distinct tissue compartments in relation to effective sinus treatment, there would not have been a reasonable expectation of successful treatment as urged by the Examiner.

Applicants, therefore, respectfully request withdrawal of the Examiner's obviousness rejections of Applicants' currently presented claims, under 35 U.S.C. §103(a), as allegedly being obvious over Shigeyama in view of Biesalski, Belloni, Popp, and further in view of Heiber.

***New claim***

New claim 29, fully supported by the originally-filed specification, has been added.

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Explicit support for new claim 29 can be found, for example, in original claims 6. No new matter has been added.

Applicants respectfully contend that all pending claims in this application are believed to be in condition for allowance.

### **CONCLUSION**

In view of the foregoing remarks, Applicants respectfully request entry of the present Response and allowance of the claim set provided herein. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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